106. (new) A composition according to claim 94, wherein the agent stimulating insulin release from β cells is repaglinide.

107. (new) The method according to claim 96, wherein the agent stimulating insulin release from β cells is repaglinide.

108. (new) A composition according to claim 97, wherein the antiobesity agent is orlistat.

109. (new) The method according to claim 99, wherein the antiobesity agent is orlistat.

REMARKS

As will be discussed in further detail below, claims 1, 2, 91, 93, 94, 96, 97 and 99 have been amended to more distinctly claim that which Applicants regard as their invention. Claims 100-109 have been added to recite specific embodiments originally claimed in claims 91-99. No new matter has been added. Therefore, new claims 100-109 are supported by the specification.

I. The Rejection of Claims 1-29, 32-37, 39, 41, 42, 44-47, 50-52, 54, 56-61, 63-73, 76, 77, 85, 86, 90, 91, 93, 94, 96, 97, and 99 under 35 U.S.C. 102(e)

Claims 1-29, 32-37, 39, 41, 42, 44-47, 50-52, 54, 56-61, 63-73, 76, 77, 85, 86, 90, 91, 93, 94, 96, 97, and 99 were rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Moller et al (US 6,262,044). This rejection is respectfully traversed.

Applicants note that in order to advance prosecution but not in acquiescence to the Examiner's position, claims 1 and 2 have been amended. The presently claimed compounds do not include those disclosed in the Moller reference. Applicants however do reserve the right to file subsequent continuation and/or divisional applications on subject matter originally encompassed by claims 1 and/or 2.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 102(e). Applicants respectfully request reconsideration and withdrawal of the rejection.

II. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: 5/21/02

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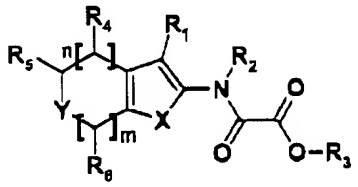
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A compound of Formula 1



Formula 1

wherein

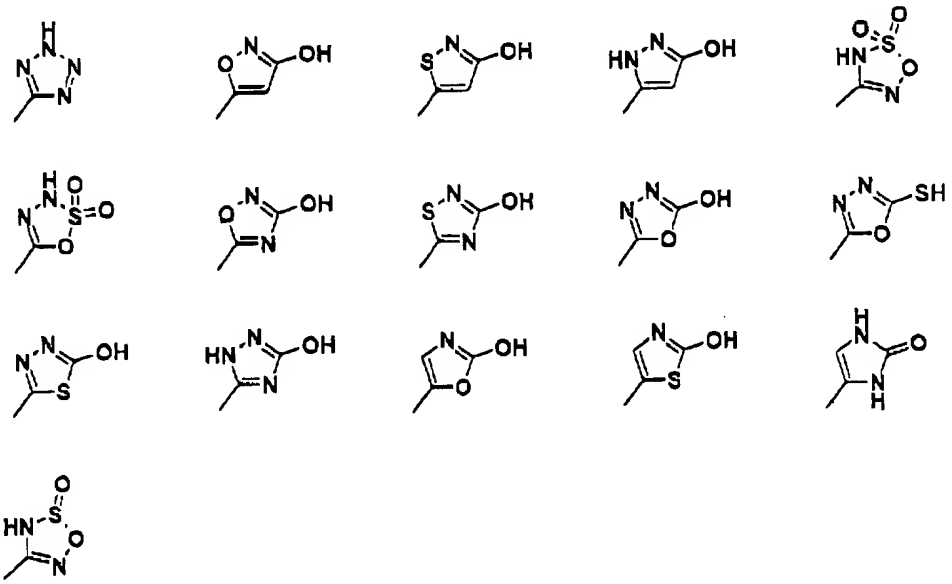
n is 0, 1 or 2;

m is 1 or 2;

X is S or O;

Y is O, S, SO or SO_2;

R_1 is selected from the group consisting of hydrogen, [or $COOR_3$, or R_1 is selected from the group consisting of the following]5-membered heterocycles selected from the group consisting of:



COOH, $COOC_1$-C_6alkyl, COOarylC_1-C_6alkyl, $COOC_1$-C_6alkylcarbonyloxyC_1-C_6alkyl [or] and $COOC_1$-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_2 is hydrogen, C_1-C_6alkyl, hydroxy or NR_7R_8;

R_3 is hydrogen, C_1-C_6alkyl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_4, R_5 and R_6 are independently hydrogen, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, aryloxyC_1-C_6alkyl, arylC_1-C_6alkyloxyC_1-C_6-alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkyl-thio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_8R_9, C_1-C_6alkylaminoC_1-C_6alkyl, aryl-C_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkyl-carbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6-alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkyl-carboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_8C_1-C_6alkylCOR_{11}, aryl$C1$-C_6alkylcarbonylamino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_7R_8$, C_1-C_6alkyl$CONR_7R_8$ or arylaminocarbonylaminoC_1-C_6alkyl; wherein the alkyl and aryl groups are optionally substituted as defined [in the section of definitions] below and R_{11} is NR_7R_8, or C_1-C_6alkylNR_7R_8;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkyl-carboxy or arylC_1-C_6alkylcarboxy wherein the alkyl and aryl groups are optionally substituted as defined in the section of definitions; or

R_7 and R_8 together with the nitrogen to which they are attached form a saturated, partially saturated or aromatic monocyclic, bicyclic or tricyclic ring system containing from 3 to 14

carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6-alkyloxyC_1-C_6alkyl, C_1-C_6alkylamino-C_1-C_6alkyl or NR_9R_{10}, wherein R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6-alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted as defined [in the section of definitions] below; or

R_7 and R_8 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

wherein the optionally substituted alkyl groups are substituted with one or more groups independently selected from halo, cyano, nitro, trihalomethyl, carbamoyl, hydroxy, oxo, $COOR_3$, $CONR_7R_8$, C_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy, thio, C_1-C_6alkylthio, arylthio, arylC_1-C_6alkylthio, NR_7R_8, C_1-C_6alkylamino, arylamino, arylC_1-C_6alkylamino, di(arylC_1-C_6alkyl)amino, C_1-C_6alkylcarbonyl, arylC_1-C_6-alkylcarbonyl, C_1-C_6alkyl-carboxy, arylcarboxy, arylC_1-C_6alkylcarboxy, C_1-C_6alkylcarbonyl-amino, -C_1-C_6alkylaminoCOR$_{12}$, arylC_1-C_6alkylcarbonylamino, tetrahydrofuranyl, morpholinyl, piperazinyl, -$CONR_7R_8$, -C_1-C_6alkyl$CONR_7R_8$, or a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam, wherein R_{12} is

C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy;

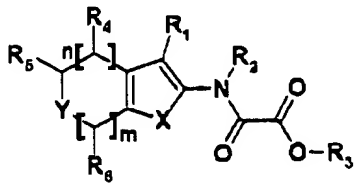
and wherein the optionally substituted aryl group is substituted with a group selected from halo, nitro, cyano, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, $COOR_3$, $CONR_7R_8$, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_7R_8, C_1-C_6-alkylamino, C_1-C_6alkylaminoC_1-C_6alkyl, arylamino, arylC_1-C_6alkylamino, arylC_1-C_6alkyl-aminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyl-carbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, carboxyC_1-C_6-alkyloxy, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_7C_1-C_6alkylCOR_{11},

arylC$_1$-C$_6$alkylcarbonylamino, arylC$_1$-C$_6$-alkylcarbonylaminoC$_1$-C$_6$alkyl, -CONR$_7$R$_8$, or -C$_1$-C$_6$alkylCONR$_7$R$_8$;

with the proviso that when R$_1$ is COOH, R$_2$, R$_3$, R$_4$, R$_5$, and R$_6$ are H, n and m are 1, and X is S, then Y is not O, S, SO or SO$_2$;
when R$_2$, R$_3$, R$_4$, R$_5$, and R$_6$ are H, n and m are 1, X is S, and Y is O, then R$_1$ is not 5-tetrazol;
when R$_1$ is COOH, R$_2$, R$_4$, R$_5$, and R$_6$ are H, n and m are 1, X is S, and Y is O, then R$_3$ is not 5-tetrazol;
when R$_1$ is COOH, R$_2$, R$_3$, R$_4$, and R$_6$ are H, n and m is 1, X is S and Y is O, then R$_5$ is not 1-oxo-1,3-dihydro-isoindol-2-yl methyl, 1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl, ((4-oxo-chromene-4H-3-carbonyl)amino)methyl, 1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl, ((4-oxo-chromene-4H-3-carbonyl)amino)methyl, ((4-oxo-chromene-4H-2-carbonyl)amino)methyl, (3-furan-3-yl-acryloylomino)methyl, (3-furan-2-yl-acryloylamino)-methyl, ((3-oxo-indane-1-carbonyl)amino)methyl, 2,4-dioxo-thiazolidin-3-ylmethyl, 3,5-dimethoxy-benzoylamino-methyl, 5,6-dichloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl, 1,3-dioxo-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl, 1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl, (4-methoxy-benzenesulfonylamino)-methyl, 2-methyl-4-oxo-4H-quinazolin-3-ylmethyl, or 1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl;
when R$_1$ is COOH, R$_2$, R$_3$, R$_4$, and R$_5$ are H, n and m are 1, X is S, and Y is O, then R$_6$ is not 1,3,-dioxo-1,3-dihydro-isoindol-2-ylmethyl or acetylamino-methyl;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, a racemic mixture, or any tautomeric form, or prodrug thereof.

2. (Amended) A compound of Formula 1



Formula 1

wherein

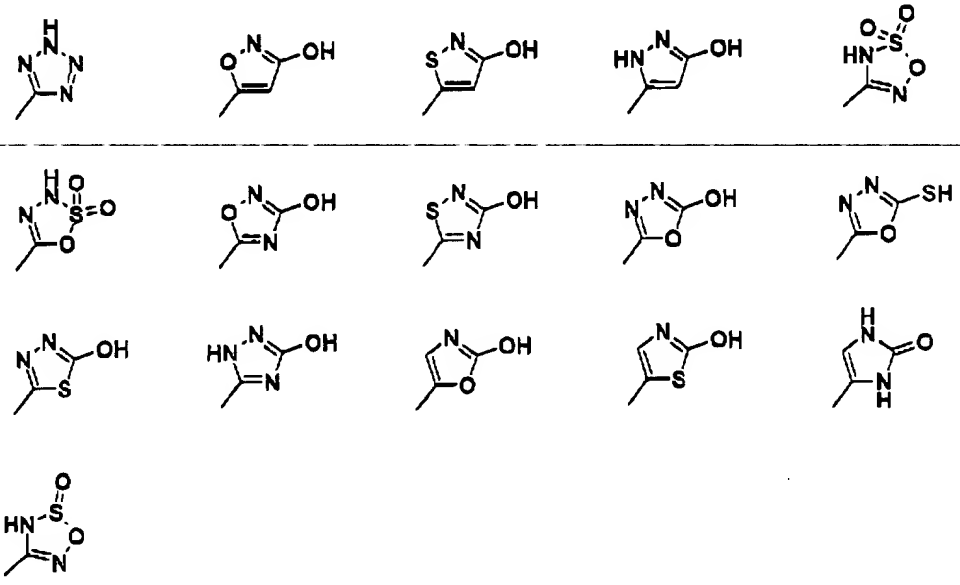
n is 0, 1 or 2;

m is 1 or 2;

X is S or O;

Y is O, S, SO or SO_2;

R_1 is selected from the group consisting of hydrogen, [or $COOR_3$, or R_1 is selected from the group consisting of the following] 5-membered heterocycles selected from the group consisting of:



COOH, $COOC_1$-C_6alkyl, $COOarylC_1$-C_6alkyl, $COOC_1$-C_6alkylcarbonyloxyC_1-C_6alkyl [or] and $COOC_1$-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_2 is hydrogen, C_1-C_6alkyl, hydroxy or NR_7R_8;

R_3 is hydrogen, C_1-C_6alkyl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_4, R_5 and R_6 are independently hydrogen, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6-alkyl, thio, C_1-C_6alkyl-thio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkyl-thio, arylC_1-C_6alkylthioC_1-C_6alkyl, [NR_8R_9,] $\underline{NR_7R_8}$, C_1-C_6alkylaminoC_1-C_6alkyl, aryl-C_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkyl-carbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6-alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl-carboxy, C_1-C_6alkylcarboxyC_1-C_6alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkyl-carboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl-aminoC_1-C_6alkyl, -carbonylNR_8C_1-C_6alkylCOR_{11}, arylC_1-C_6alkyl-carbonyl-amino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_7R_8$, or C_1-C_6alkyl-$CONR_7R_8$ wherein the alkyl and aryl groups are optionally substituted and R_{11} is NR_7R_8, or C_1-C_6alkylNR_7R_8;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy wherein the alkyl and aryl groups are optionally substituted; or
R_7 and R_8 together with the nitrogen to which they are attached form a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6-alkyloxyC_1-C_6alkyl, C_1-C_6alkylamino-C_1-C_6alkyl or NR_9R_{10}, wherein R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6-alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or
R_7 and R_8 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

with the proviso that when R_1 is COOH, R_2, R_3, R_4, R_5, and R_6 are H, n and m are 1, and X is S, then Y is not O, S, SO or SO_2;

when R_2, R_3, R_4, R_5, and R_6 are H, n and m are 1, X is S, and Y is O, then R_1 is not 5-tetrazol;

when R_1 is COOH, R_2, R_4, R_5, and R_6 are H, n and m are 1, X is S, and Y is O, then R_3 is not 5-tetrazol;

when R_1 is COOH, R_2, R_3, R_4, and R_6 are H, n and m are 1, X is S and Y is O, then R_5 is not 1-oxo-1,3-dihydro-isoindol-2-yl methyl, 1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl, ((4-oxo-chromene-4H-3-carbonyl)amino)methyl, 1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl, ((4-oxo-chromene-4H-3-carbonyl)amino)methyl, ((4-oxo-chromene-4H-2-carbonyl)amino)methyl, (3-furan-3-yl-acryloylomino)methyl, (3-furan-2-yl-acryloylamino)-methyl, ((3-oxo-indane-1-carbonyl)amino)methyl, 2,4-dioxo-thiazolidin-3-ylmethyl, 3,5-dimethoxy-benzoylamino-methyl, 5,6-dichloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl, 1,3-dioxo-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl, 1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl, (4-methoxy-benzenesulfonylamino)-methyl, 2-methyl-4-oxo-4H-quinazolin-3-ylmethyl, or 1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl;

when R_1 is COOH, R_2, R_3, R_4, and R_5 are H, n and m are 1, X is S, and Y is O, then R_6 is not 1,3,-dioxo-1,3-dihydro-isoindol-2-ylmethyl or acetylamino-methyl;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, a racemic mixture, or any tautomeric form.

91. (Amended) A [pharmaceutical] composition comprising an effective amount of a compound of claim 1 together with one or more pharmaceutically acceptable carriers or diluents and an insulin sensitizer[, such as a thiazolidinedione eg. troglitazone, ciglitazone, pioglitazone, rosiglitazone, 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, preferably the potassium salt, or (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salts thereof, preferably the arginine salt].

93. (Amended) A method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising administering to a subject in need thereof an effective amount of a compound of claim 1 and an insulin sensitizer[, such as a thiazolidinedione eg. troglitazone, ciglitazone, pioglitazone, rosiglitazone, 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, preferably the potassium salt, or (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt thereof, preferably the arginine salt] to said subject.

94. (Amended) A [pharmaceutical] composition comprising an effective amount of a compound of claim 1 together with one or more pharmaceutically acceptable carriers or diluents and an agent stimulating insulin release from β cells[, such as repaglinide].

96. (Amended) A method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising administering to a subject in need thereof an effective amount of a compound according to claim 1 and an agent stimulating insulin release from β cells[such as repaglinide].

97. (Amended) A [pharmaceutical] composition comprising a compound of claim 1 together with one or more pharmaceutically acceptable carriers or diluents and an antiobesity agent[such as orlistat].

99. (Amended) A method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising administering to a subject in need thereof an effective amount of a compound of claim 1 and an antiobesity agent[such as orlistat].